

Appl. No. 09/787,632
Amdt. dated December 8, 2003
Reply to Office Action of October 16, 2003

REMARKS/ARGUMENT

This amendment responds to the Office Action of October 16, 2003.

Claims 7, 11-17, and 19-23 are pending in the application. The specification has been amended at the points indicated to correct the recitations of the Colby formula, which, through inadvertent error, were incorrectly modified in the response to the previous Office Action. The undersigned apologizes for his error and regrets any inconvenience this may have caused the Patent and Trademark Office. Entry of these amendments is respectfully requested as it is believed they put the application in condition for allowance or in better condition for appeal.

The amendment filed August 6, 2003 has been objected to under 35 U.S.C. 132 for introducing new matter into the disclosure. As noted above, the Colby formula was erroneously amended in the response. The error is corrected by the above amendments to the specification. Accordingly, it is requested that the objection under 35 U.S.C. 132 be withdrawn.

Claims 7, 11-17, and 19-23 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Latorse (WO96/03044), Shibata et al. (EP 0775 696 A1), and Seitz et al. (EP 0472 996 A1) in view of Budavari (Merck Index, 11th ed., 1989, monograph 4964, page 803).

It has been pointed out in the application on page 1, at lines 15-21 that international patent application WO 96/03044 also discloses a certain number of fungicidal compositions comprising a 2-imidazolin-5-one in combination with one or more fungicidal active materials and that patent applications EP-A-0,775,696 and EP-A-0,472,966 present novel compounds for fungicidal use which have an amino acid amide structure. Also, on page 5, at lines 14-23, it is stated:

"Compound (I) is known, in particular, from patent application EP-A-0,629,616.

Compound (II), when A represents the group A1, and its use as a fungicide are described in particular in European patent application EP-A-0,775,696.

Compound (II), when A represents the group A2, and its use as a fungicide are described in particular in European patent application EP-A-0,472,996."

Patent application EP-A-0,629,616 is understood to be an equivalent of international patent application WO 96/03044.

Compound (II), when A represents the group A2, is outside the scope of the pending claims. Accordingly, it is submitted that the rejection, insofar as it is dependent upon European patent application EP-A-0,472,996, is moot and no further discussion of this reference is necessary.

Budavari merely shows that iprodione, which can, if desired, be used in combination with Compound (I) and Compound (II), is a known fungicide.

Thus, Latorse discloses a fungicidal compound that corresponds to Compound (I) of the present invention and further discloses its use in combination with a second fungicidal compound, which can be a derivative of dithiocarbamic acid or its salts, a derivative of phosphorous acid, a chlorinated derivative of benzene, a derivative comprising a heterocycle containing from 1 to 2 nitrogen atoms, a derivative of a triazole, a dicarboximide derivative, copper or an organic or inorganic derivative thereof, an amide, a morpholine derivative, a derivative of the methoxyacrylate type, a guanidine derivative, or a derivative of the phenylbenzamide type.

Nowhere among these is there a disclosure or suggestion of the currently claimed N¹-[(R)-1-(6-fluoro-2-benzothiazolyl)ethyl]-N²-isopropoxycarbonyl-L-valinamide. The closest the reference comes is the disclosure of amides, but the only operable amides disclosed are cymoxanil, metalaxyl, and oxadixyl.

Similarly, Shibata et al. disclose N¹-[(R)-1-(6-fluoro-2-benzothiazolyl)ethyl]-N²-isopropoxycarbonyl-L-valinamide, but only state that it can be used in combination "with other fungicides" without any indication of what such fungicides might be.

It is understood to be the Examiner's position that Compound (I) is a known fungicide and Compound (II) is a known fungicide and, thus, it would be obvious to use them in combination. However, as the Examiner has pointed out previously, "Synergism is an unexpected and highly unpredictable effect."

It is the Applicants' position that they have discovered a combination, i.e., (4-S)-4-methyl-2-methylthio-4-phenyl-1-phenylamino-2-imidazolin-5-one and N¹-[(R)-1-(6-fluoro-2-benzothiazolyl)ethyl]-N²-isopropoxycarbonyl-L-valinamide, that clearly exhibits synergism. They have demonstrated this synergism for this combination in each of Examples 1 through 4 of the application, using means for determining synergism that is accepted in the art, i.e., the Colby formula, which was published in the journal Weeds, 1967, 15, pp. 20-22. Thus, they have shown synergism for the claimed combination of compounds and "synergism is an unexpected and highly unpredictable effect". Accordingly, unexpected results have been shown for the claimed combination and it logically follows from this that the combination cannot be obvious.

It is believed the following table and explanation will serve to clarify the data present in the examples that show the synergism provided by the present invention.

Example 1			
Active Ingredients	% of Inhibition (PE)	Colby E (expected % of Inhibition, TE)	Conclusion
Compound A	51.8	--	Synergy
Compound B	48	--	
Compounds A + B	90.3	75	

In the conclusion to Example 1 in the specification (page 32, lines 19-22) it is stated, "In this test, the composition according to the invention showed a practical efficacy of 90.3%, whereas the theoretical efficacy, calculated by the Colby formula, gave a value of 75.0%."

The theoretical efficiency for the combination is calculated as follows:

$$\%TE (A+B) = \%PE(A) + \%PE(B) - (\%PE(A) \times \%PE(B) / 100)$$

$$\%TE (A+B) = 51.8 + 48 - (51.8 \times 48 / 100)$$

$$\%TE (A+B) = 99.8 - 24.8 = 75$$

However, the actual efficiency of the combination (i.e., the practical efficiency) was found by experimentation to be higher than 75, i.e., 90.3, thereby showing the synergism of the claimed combination of Compound A and Compound B.

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Example 3			
Active Ingredients	% of Inhibition (15 / 23 / 26 Days)	Colby E (expected % of Inhibition)	Conclusion
Compound A	27.5 / 12.5 / 12.5	--	Synergy
Compound B	27.5 / 7.5 / 5.0	--	
Compounds A + B	76.2 / 52.5 / 40.0	47.4 / 19.1 / 16.9	

Similar to the above, in Example 3, after 15 days, the calculation shows:

$$\%TE (A+B) = 27.5 + 27.5 - (27.5 \times 27.5 / 100)$$

$$\%TE (A+B) = 55.0 - 7.6 = 47.4$$

However, the actual efficiency of the combination (i.e., the practical efficiency) was found by experimentation to be higher than 47.4, i.e., 76.2, thereby showing the synergism of the claimed combination of Compound A and Compound B, as pointed out in the specification as filed in the Table on page 36.

Similar calculations can be carried out for the data after 23 and 26 days in Example 3 and after 5 and 8 days in Example 4.

Example 4			
Active Ingredients	% of Inhibition (5 / 8 Days)	Colby E (expected % of Inhibition)	Conclusion
Compound A	9.4 / 10.7	--	Synergy
Compound B	38.2 / 35.7	--	
Compounds A + B	66.1 / 62.3	44 / 42.6	

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Thus, each of the examples in the application as filed has shown synergism when the compounds of the present claims are employed in combination.

In the Office Action, the Examiner stated:

"The data provided by Applicants does not clearly and convincingly demonstrate synergism for any combination within the claims and is not reasonably commensurate in scope with the instant claims. For example, examples 1 to 4 in page 31 to 38 in the specification relate only to certain fungal species and the employment of 3 compounds herein claimed useful in a fungicidal combination in accordance with the claims (i.e., compound A, B, and C in the specification). A supraadditive effect for the combinations of individual agents herein, based on raw data on the same individual agents in comparison to their corresponding combination, is not present. It is not clear what the practical efficacy of compound A and that of compound B are, and therefore, it is not possible to evaluate what the theoretical efficacy according to Colby's formula, will be. Moreover, the unexpected results have to be commensurate with the scope of the subject matter claimed. In the instant case, claim recites the ratio between compound A and compound B as the range from 5 to 0.5, while the examples 1-4 in the instant specification merely demonstrate the ratio of 1:1 to 1:4. In addition, it is not clear why the theoretical efficacy formula disclosed in page 32, line 18, for example, as $\%TE(A+B) = \%TE(A) + \%TE(B) (\%PE(A) \times \%PE(B)/100)$. Should $\%TE(A+B)$ be equal to $\underline{\%PE(A) + \%PE(B)} - (\%PE(A) \times \%PE(B)/100)$ instead?"

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The answer to the Examiner's last question is "Yes", and, as noted above, this is being corrected by the above amendment.

As pointed out above, it is the Applicants position that Examples 1-4 clearly show, both in the written material presented and in the accompanying Tables, the synergistic effects of the combination of the present claims, as determined by the Colby formula. They have provided examples of two different fungi, downy mildew of grapevine (*Plasmopara viticola*) and late blight of potato (*Phytophthora infestans*). Additionally, there is an extensive teaching in the specification, beginning on page 28, of those fungi that can be treated with the fungicides of the present invention. It is submitted that more than this is not required.

Further, the Examiner is incorrect in saying that the ratio between compound A and compound B, claimed to be from 5 to 0.5, merely demonstrate the ratio of 1:1 to 1:4 in the examples 1-4. In Example 1, the A:B ratio is approximately 3.33; see page 31, lines 15-16. In Example 2, the A:B ratio is 2; see page 33, lines 6-8. In Example 3, the A:B ratio is 4; see page 35, lines 1-3; and in Example 4, the A:B ratio is also 4; see page 36, lines 13-15. Thus, the ratios of compound A to compound B illustrated by the Examples range from 2:1 to 4:1, and not 1:1 to 1:4, as stated by the Examiner. It is submitted that this is adequate to support a claim to the range 5 to 0.5, particularly in the light of the disclosure on page 8 that persons skilled in the art would be entirely capable of carrying out additional tests to find other values of the ratio of doses of the compounds of the invention for which a synergistic effect would be observed.

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It is therefore requested that the rejection of claims 7, 11-17, and 19-23 under 35 U.S.C. 103(a) as being unpatentable over Latorse, Shibata et al., and Seitz et al. in view of Budavari be withdrawn.

In view of the foregoing, it is submitted that this application is in condition for allowance and an early Office Action to that end is earnestly solicited.

Respectfully submitted,



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